Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls

Christoph U. Correll[1-5], Marco Solmi[5-7], Nicola Veronese[5], Beatrice Bortolato[5,8], Stella Rosson[6], Paolo Santonastaso[6], Nita Thapa[9], Michele Fornaro[10], Davide Gallicchio[6], Enrico Collantoni[6], Giorgio Pigato[6], Angela Favaro[6], Francesco Monaco[5], Cristiano Kohler[11], Davy Vancampfort[12,13], Philip B. Ward[14], Fiona Gaughran[15], André F. Carvalho[5,11], Brendon Stubbs[5,15-17]

[1]Psychiatry Research, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [2]Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, USA; [3]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA; [4]Department of Psychiatry and Behavioral Medicine, Albert Einstein College of Medicine, Bronx, NY, USA; [5]Institute for Clinical Research and Education in Medicine, Padua, Italy; [6]Department of Neurosciences, University of Padua, Padua, Italy; [7]Mental Health Department, Local Health Unit 17, Padua, Italy; [8]Mental Health Department, Local Health Unit 10, Portogruaro, Italy; [9]Kaski Sewa Hospital & Research Centre, Pokhara, Nepal; [10]New York Psychiatric Institute, Columbia University, New York, NY, USA; [11]Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, Brazil; [12]KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium; [13]KU Leuven University Psychiatric Center, Leuven-Kortenberg, Belgium; [14]School of Psychiatry, University of New South Wales, Sydney, Australia; [15]South London and Maudsley, NHS Foundation Trust, London, UK; [16]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [17]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

People with severe mental illness (SMI) – schizophrenia, bipolar disorder and major depressive disorder – appear at risk for cardiovascular disease (CVD), but a comprehensive meta-analysis is lacking. We conducted a large-scale meta-analysis assessing the prevalence and incidence of CVD; coronary heart disease; stroke, transient ischemic attack or cerebrovascular disease; congestive heart failure; peripheral vascular disease; and CVD-related death in SMI patients (N=3,211,768) versus controls (N=113,383,368) (92 studies). The pooled CVD prevalence in SMI patients (mean age 50 years) was 9.9% (95% CI: 7.4-13.3). Adjusting for a median of seven confounders, patients had significantly higher odds of CVD versus controls in cross-sectional studies (odds ratio, OR=1.53, 95% CI: 1.27-1.83; 11 studies), and higher odds of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66). People with major depressive disorder were at increased risk for coronary heart disease, while those with schizophrenia were at increased risk for coronary heart disease, cerebrovascular disease and congestive heart failure. Cumulative CVD incidence in SMI patients was 3.6% (95% CI: 2.7-5.3) during a median follow-up of 8.4 years (range 1.8-30.0). Adjusting for a median of six confounders, SMI patients had significantly higher CVD incidence than controls in longitudinal studies (hazard ratio, HR=1.78, 95% CI: 1.60-1.98; 31 studies). The incidence was also higher for coronary heart disease (HR=1.54, 95% CI: 1.30-1.82), cerebrovascular disease (HR=1.64, 95% CI: 1.26-2.14), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24). People with major depressive disorder, bipolar disorder and schizophrenia were all at increased risk of CVD-related death versus controls. CVD incidence increased with antipsychotic use (p=0.008), higher body mass index (p=0.008) and higher baseline CVD prevalence (p=0.03) in patients vs. controls. Moreover, CVD prevalence (p=0.007), but not CVD incidence (p=0.21), increased in more recently conducted studies. This large-scale meta-analysis confirms that SMI patients have significantly increased risk of CVDs and CVD-related mortality, and that elevated body mass index, antipsychotic use, and CVD screening and management require urgent clinical attention.

Key words: Cardiovascular disease, severe mental illness, schizophrenia, bipolar disorder, major depression, coronary heart disease, cerebrovascular disease, congestive heart failure, premature mortality

People with severe mental illness (SMI) – including schizophrenia, bipolar disorder, major depressive disorder, and their related spectrum disorders – have a life expectancy shortened of 10-17.5 years compared to the general population[1,2]. While suicide explains some of this reduced life expectancy[3], it is now established that physical diseases account for the overwhelming majority of premature mortality[4,5]. Among physical conditions, cardiovascular disease (CVD) is the main potentially avoidable contributor to early deaths in patients with SMI[4].

Given the importance of understanding the magnitude, contributors to and relative distribution of CVD risk in people with SMI, a number of disease-specific meta-analyses investigated if people with major depressive disorder, bipolar disorder or schizophrenia are at an increased risk of CVD compared to controls. These meta-analyses reported that people with depression (defined by the presence of depressive symptoms or a diagnosis of major depressive disorder) are at increased CVD risk[6,7], including stroke (risk ratio, RR=1.34, 95% CI: 1.17-1.54), myocardial infarction (hazard ratio, HR=1.31, 95% CI: 1.09-1.57), coronary heart disease (RR=1.36, 95% CI: 1.24-1.49) and coronary heart disease-related death (HR=1.36, 95% CI: 1.14-1.63)[6-8]. While clearly informative, results concerning CVD were not specific for major depressive disorder defined according to established diagnostic criteria, possibly biasing such observed association towards a lower risk[9]. Another meta-analysis of longitudinal studies, which utilized standardized criteria to define bipolar disorder, reported mixed results, since people with that disorder were actually not at increased risk of myocardial infarction (RR=1.09, 95% CI: 0.96-1.24), whereas the risk of stroke was higher compared to controls (RR=1.74, 95% CI: 1.29-2.35)[10]. Among individuals with schizophrenia, previous meta-analyses[11,12] reported an overall increased risk of CVD compared to controls (RR=1.53, 95% CI: 1.27-1.86). This risk increase included stroke (up to RR=1.71, 95% CI: 1.19-2.46) and heart failure (RR=1.81, 95% CI: 1.42-2.29), but not coronary heart disease (RR=1.20, 95% CI: 0.93-1.53).

While the existing literature has provided relevant insights, several limitations are to be highlighted and important questions remain unanswered. First, some of the previous meta-analyses did not use standardized clinical assessments to identify and categorize SMI and/or cardiovascular events. Second, the exact prevalence and incidence of each type of CVD among people with SMI, both within and across major diagnostic SMI subgroups, remains unclear. Third, the magnitude of premature CVD-related mortality risk in people with SMI versus controls is to be specified. Fourth, potential risk factors for increased CVD and related mortality risk across the SMI groups have not been elucidated via meta-analytic techniques, which could help identify targets for treatment guidelines, clinical standards and development of preventive and therapeutic programs. In this regard, large-scale pooled analyses in the SMI population can provide relevant information, allowing the investigation of potentially shared risk factors across many studies and participants, thus dissecting CVD risk factors associated with SMI and/or treatments for these disorders from factors which are non-specific or shared with the general population[13]. Additionally, pooling of data

allows for the investigation of demographic, regional and treatment variables, both within and across major diagnostic categories.

Given the caveats mentioned above, the current gaps within the literature and the need to better understand CVD risk among people with SMI, we conducted a large scale meta-analysis investigating the prevalence, incidence and mortality attributed to CVD and their correlates among people with SMI, both within and across major diagnostic groups.

METHODS

This systematic review and meta-analysis adhered to the PRISMA statement[14], following a predetermined, but unpublished protocol.

Search strategy

An electronic literature search was conducted in PubMed, Embase and Scopus from database inception until August 2, 2016 by two independent reviewers, using the search terms ("bipolar disorder" OR mania OR schizophrenia OR schizoaffective OR psychosis OR “major depression” OR “serious mental illness”) AND (cardiovascular OR stroke OR cerebrovascular OR "transient ischemic attack" OR "transient ischaemic attack" OR “peripheral vascular” OR "myocardial infarction" OR "coronary heart disease” OR” coronary artery disease” OR “ischemic heart disease” OR “ischaemic heart disease” OR "hypertensive heart disease" OR angina OR “cardiac failure” OR “heart failure” OR “congestive heart failure” OR “atrial fibrillation” OR "pulmonary embolism" OR “cardiovascular mortality”). Furthermore, bibliographies of included papers were reviewed.

Inclusion and exclusion criteria

We included studies with the following characteristics: a) reporting on patients with schizophrenia, schizophrenia or schizoaffective disorder, bipolar disorder or bipolar spectrum disorders, major depressive disorder or depressive episodes, or SMI (defined as at least two among major depressive spectrum, bipolar spectrum and schizophrenia spectrum disorders) according to DSM-III, DSM-IV, DSM-5, ICD-8, ICD-9 or ICD-10, or a medical record diagnosis based on a clinical interview; b) having a cross-sectional or a retrospective/prospective longitudinal design, either with or without a control group; c) using a standardized definition of CVD; d) reporting RR, HR or odds ratio (OR) comparing patients with region-specific controls, percentage or number of events at baseline (data used for cross-sectional analysis = prevalence) and/or follow-up (data used for longitudinal analysis = cumulative incidence).

We excluded studies that investigated cardiovascular risk estimates and/or factors, subclinical CVD, or SMI rates in populations with CVD. In case of multiple publications from the same study, only the most recent paper or the article with the longest follow-up was included. When required, we contacted the primary/corresponding authors of potential studies to confirm eligibility or acquire unpublished variables of interest.

Data extraction

Seven authors divided in four pairs independently extracted data in a standardized Microsoft Excel sheet, with reciprocal validation of data extraction results. The extracted data included: authors, year and country; geographic region; study design; data source; period of data collection; SMI diagnostic criteria; CVD diagnostic criteria; specific SMI and CVD diagnosis; case and control inclusion criteria; number of cases and controls; percentage or number with CVD, coronary heart disease, cerebrovascular disease and congestive heart failure at baseline; number of events at follow-up; follow-up duration; number and type of covariates considered in the analyses; OR, RR, rate ratio and HR with their respective 95% upper and lower CIs; mean age with standard deviation; mean body mass index with standard deviation; proportion of males; co-occurring obesity, alcohol and substance related disorders, diabetes, hypertension, and hyperlipidemia; married status; employment status; percentage of patients with poorest income and least urbanized; and percentage of patients taking antipsychotics. Rate ratios calculated with Cox regression models were included in HR analyses. When authors did not specify whether or not a rate ratio had been calculated with Cox regression models, we contacted them seeking clarification.

Outcomes

Primary outcomes were CVD prevalence and cumulative incidence plus CVD-related mortality in people with SMI, as well as adjusted OR for prevalence and HR for incidence rates in SMI versus controls. Secondary outcomes were the same measures for specific CVDs (i.e., coronary heart disease, cerebrovascular disease, congestive heart failure) in SMI patients, as well as adjusted OR and HR versus controls.

Prevalence and OR were calculated from cross-sectional studies and from baseline results of longitudinal studies. Where available, incidence, RR and HR were calculated from longitudinal studies.

Quality assessment

For the purpose of this meta-analysis, a checklist (yes versus no) was used to assess the methodological quality of included studies. The evaluation of methodological quality across studies was based on the following factors: clear diagnostic criteria, presence of a control group, matching of the control group, covariate-adjusted outcomes, reported cardiovascular risk factors at baseline, and follow-up ≥5 years.

Data analysis

This meta-analysis was performed using Comprehensive Meta-Analysis V3[15]. All outcomes were meta-analyzed when at least two studies provided data. A random effects model[16,17] was used to account for between-study heterogeneity. We calculated pooled CVD prevalences and pooled CVD cumulative incidences, each with SMI subgrouping. For dichotomous primary and secondary outcomes comparing pooled SMI and SMI subgroups with controls, we calculated unadjusted as well as adjusted pooled OR for cross-sectional data, and unadjusted pooled RR, as well as adjusted pooled HR, for longitudinal data. Funnel plots were visually inspected, and Egger's test[18] and Begg-Mazumdar Kendall's tau[19] were used to determine if publication bias was likely. When publication bias was present, the trim and fill[20] procedure was run to evaluate if the results changed after imputing potentially missing studies.

Between-study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p<0.05$ and I-squared ≥50% indicating significant heterogeneity[21]. To identify potential moderators, meta-regression was run with Comprehensive Meta-Analysis V3 for unadjusted outcomes where heterogeneity was significant.

Since CVD rates in the general population vary across the world, we also performed a stratified analysis across geographic regions (Asia, Europe, North America, Oceania) regarding raw CVD prevalence and incidence in SMI populations, and compared patients to their respective region-specific general population controls (calculating RRs as well as adjusted ORs and HRs for the four regional strata and comparing them across the different regions whenever at least two studies provided data per each region).

The following study and patient characteristics were explored as potential moderators and mediators in addition to SMI status: geographical region of the sample; time of data collection; percentage of patients taking antipsychotics; and the difference between patient and control samples regarding age, body mass index; proportion of males and of those with married status, unemployed, with poorest income, least urbanized, and having co-occurring obesity, alcohol and substance-related disorders, diabetes, hypertension or hyperlipidemia.

RESULTS

Search results

Out of 18,064 initial hits across the searched electronic databases, 11,878 unduplicated hits were screened, and 11,576 were excluded through title/abstract reading. Altogether, 302 full texts were reviewed, and 210 were excluded with specific reasons. Among 92 studies meeting inclusion criteria, 27 had a cross-sectional design[22-48] and 65 studies had a retrospective or prospective longitudinal design[49-113] (Figure 1).

Characteristics of included studies

We included 92 studies, with a total population of 3,211,768 patients (mean age 50 years, 49% male) with SMI and 113,383,368 controls (mean age 51 years, 49% male), with a total of 116,595,136 subjects when summing those studies where patient and control sample sizes were not separately reported. Altogether, 27 studies (N=27,037,943) were cross-sectional and 65 studies (N=89,557,193) were longitudinal. Overall, 38 studies included patients with schizophrenia (of which 29 were longitudinal), 30 with bipolar disorder (21 longitudinal), 30 with major depressive disorder (22 longitudinal), and 14 with SMI (8 longitudinal). Taken together, six studies included only patients with SMI (N=884,412), 16 studies included only patients with bipolar disorder (N=71,832), 20 studies included only patients with major depressive disorder (N=111,360), and 29 studies included only patients with schizophrenia (N=1,591,106), while 19 studies included different subgroups of SMI, providing data for each of them separately (some studies included more than one diagnostic group, see Tables 1 and 2 for details).

Meta-analysis: cross-sectional results

The pooled CVD prevalence in SMI was 9.9% (95% CI: 7.4-13.3; 38 studies). Individual rates were 8.4% for people with bipolar disorder (95% CI: 5.4-12.6, 12 studies, N=66,911); 11.7% for those with major depressive disorder (95% CI: 3.6-32.2, 7 studies, N=83,965); 11.8% for those with schizophrenia (95% CI: 7.1-19.0, 13 studies, N=191,982), and 11.8% for those with SMI (95% CI: 4.1-29.4, 6 studies, N=17,286) ($p<0.001$ for SMI diagnostic subgroup comparisons).

Adjusting for a median of seven potential confounders, the adjusted pooled OR for CVD in SMI compared to controls was 1.53 (95% CI: 1.27-1.83, $p<0.001$, 11 studies). For specific CVDs, pooled together, people with SMI had an increased risk of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55, $p<0.001$, 5 studies) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66, $p<0.001$, 6 studies), with a strong statistical trend for congestive heart failure (OR=1.28, 95% CI:

0.99-1.65, p=0.06, 4 studies). Considering separately single types of SMI and CVD, in adjusted OR analyses, bipolar disorder was not significantly associated with CVD or its subtypes; major depressive disorder was significantly associated with CVD and coronary heart disease; and schizophrenia was significantly associated with coronary heart disease, cerebrovascular disease and congestive heart failure (Table 3). No adjusted ORs were available for mixed SMI groups.

All significant results were significantly heterogeneous. After adjusting for publication bias with the trim-and-fill method, all pooled previously significant ORs remained statistically significant, confirming the association of CVD, coronary heart disease and cerebrovascular disease with SMI, while the OR for congestive heart failure became marginally significant (p=0.05).

Meta-analysis: longitudinal adjusted results

Among patients with SMI, 3.6% (95% CI: 2.7-5.3%) experienced a CVD event during a median follow-up period of 8.4 years (range 1.8-30.0) (65 studies). After adjusting for a median of six potential confounders, people with SMI were at significantly increased risk across longitudinal studies for CVD (HR=1.78, 95% CI: 1.60-1.98) (31 studies, N=671,384 cases vs. N=14,335,203 controls) as well as for specific CVDs, including coronary heart disease (HR=1.54, 95% CI: 1.30-1.82, 18 studies, N=194,017 cases vs. N=13,530,858 controls), cerebrovascular disease (HR=1.64, 95% CI: 1.26-2.14, 11 studies, N=188,841 cases vs. N=13,113,564 controls), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70, 2 studies, N=409 cases vs. N=41,678 controls), peripheral vascular disease (only unadjusted RR=3.11, 95% CI: 2.46-3.91, three studies), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24, 16 studies, N=353,407 cases vs. N=7,317,053 controls).

According to adjusted HRs, schizophrenia was significantly associated with CVD in longitudinal studies (HR=1.95, 95% CI: 1.41-2.70, 14 studies), as well as with coronary heart disease (HR=1.59, 95% CI: 1.08-2.35, 5 studies), cerebrovascular disease (HR=1.57, 95% CI: 1.09-2.25, 5 studies), and CVD-related death (HR=2.45, 95% CI: 1.64-3.65, 9 studies).

According to adjusted HRs, bipolar disorder was significantly associated with CVD in longitudinal studies (HR=1.57, 95% CI: 1.28-1.93, 10 studies) as well as with CVD-related death (HR=1.65, 95% CI: 1.10-2.47, 3 studies), with a trend toward a significant association with cerebrovascular disease (HR=1.60, 95% CI: 0.99-2.57, 4 studies), but no significant association with coronary heart disease (HR=1.16, 95% CI: 0.76-1.78, 4 studies).

According to adjusted HRs, major depressive disorder was significantly associated with CVD in longitudinal studies (HR=1.72, 95% CI: 1.48-2.00, 18 studies) as well as with coronary heart disease (HR=1.63, 95% CI: 1.33-2.00, 9 studies), cerebrovascular disease (HR=2.04, 95% CI: 1.05-3.96, 3 studies), congestive heart failure (HR=2.02, 95% CI: 1.48-2.75, 2 studies), and CVD-related death (HR=1.63, 95% CI: 1.25-2.13, 7 studies).

According to adjusted HRs, mixed SMIs were significantly associated with CVD in longitudinal studies (HR=3.24, 95% CI: 2.15-4.88, 3 studies) as well as with CVD-related death (HR=2.75, 95% CI: 1.32-5.73, 3 studies).

All significant results were significantly heterogeneous, except for mixed SMI and CVD risk, as well as all the congestive heart failure results. After trim and fill procedure, all results remained unchanged, and Egger test did not show any evidence of publication bias influencing the results (see Table 4 for details).

Quality assessment of included studies

Quality ratings of single studies are presented in Table 5. All studies used clear diagnostic criteria, by design. Among the 27 cross-sectional studies, all except 9 studies had a control group, 5 studies used a matched control sample, 13 studies adjusted analyses for relevant covariates, and all except 6 studies reported cardiovascular risk factors. Among the 65 longitudinal studies, all had a control group, which was matched in all but 12 studies, only 19 studies adjusted for covariates, 38 studies reported on cardiovascular risk factors, and all except 12 studies had a follow-up of at least 5 years.

Regional CVD prevalence, incidence and longitudinal risk

Raw CVD prevalence and incidence rates consistently increased from Asia, through Europe and North America, to Oceania (Asia: 5.4% and 2.6%; Europe: 9.7% and 3.4%; North America: 14.6% and 4.6%; Oceania: 20.6% and 26.3%; $p<0.0001$ for both prevalence and incidence). However, when comparing CVD risk in SMI patients in each region with their respective control groups, there was no statistically significant difference anymore across regions, with both RRs and adjusted HRs showing comparably increased CVD incidence risk in the SMI population (RRs ranging from 1.17 in Europe to 1.63 in Asia, $p=0.08$; and HRs ranging from 1.58 in Oceania to 1.88 in both Europe and North America, $p=0.29$) (Table 6). There were insufficient numbers of studies to perform this analysis for adjusted ORs regarding prevalence rates across regions, or for adjusted ORs, RRs or HRs pertaining to specific CVD subgroups.

Meta-regression

Due to heterogeneous or partial reporting of possible moderator variables in the included studies, all meta-regression analyses were based on a much reduced number of studies. Hence, all analyses were less powered in comparison with the large sets of data used for cross-sectional prevalence and longitudinal incidence analyses. Nonetheless, CVD incidence increased

significantly with a higher percentage of patients using antipsychotics (12 studies; β=0.04, 95% CI: 0.01-0.08, p=0.008), higher baseline body mass index in patients vs. controls (6 studies; β=0.24, 95% CI: 0.06-0.42, p=0.008), and higher CVD prevalence at baseline in patients vs. controls (7 studies; β=0.07, 95% CI: 0.01-0.14, p=0.03). CVD prevalence increased in more recent studies (38 studies; β=0.07, 95% CI: 0.02-0.12, p=0.007), whereas the same was not true for CVD incidence (65 studies; β=–0.02, 95% CI=–0.07 to 0.01, p=0.21).

DISCUSSION

To our knowledge, this is the first large scale meta-analysis providing comprehensive quantitative data on the prevalence and incidence of CVD in people with SMI, including both pooled data and comparisons across CVD and SMI diagnostic subgroups. Our results establish that approximately 10% of people with SMI with a mean age of 50 years have at least one comorbid CVD. Moreover, our longitudinal analysis documents a 3.6% incidence rate of CVD during a median of 8.4 years of follow-up. Patients with SMI show a 53% higher risk for having CVD, a 78% higher risk for developing CVD, and an 85% higher risk of death from CVD compared to the regionally matched general population.

This study provides a worldwide epidemiologic representation of CVD prevalence and incidence rates in SMI, reporting the lowest absolute prevalence and incidence in Asia, increasing through Europe and North America, and reaching the highest levels in Oceania. However, in analyses with sufficient numbers of available studies, neither RRs nor adjusted HRs indicated significantly different CVD incidence risk across regions, meaning that SMI patients are at an increased risk across the world and that CVD risk-reducing interventions in SMI are needed with the same urgency across all regions of the world. Moreover, while the prevalence and incidence of each CVD in people with SMI show some minor variations, people with major depressive disorder, bipolar disorder and schizophrenia are clearly all at an increased risk of CVD-related deaths compared to population-stratified controls, calling for urgent action.

We were able to identify some important and actionable moderators of increased CVD risk, including antipsychotic use, elevated body mass index and elevated baseline CVD. Based on these results, it is imperative that clinicians: a) only utilize antipsychotics, particularly for non-psychotic conditions, when alternative treatment options with lower CVD risk potential have been tried sufficiently; and b) screen for and manage emerging and existing CVDs as well as their risk factors, including weight gain and elevated body mass index. Our data, adding to research demonstrating a significantly higher prevalence of metabolic syndrome in people with SMI compared to controls[114], clearly suggest there is an urgent need to prevent and manage CVD risk in this population.

Our results demonstrating a higher CVD prevalence in SMI populations versus controls in more recent studies are also concerning, as it supports accumulating data indicating that secondary prevention has been much less successful in the SMI population that in the general population, leading to a widening of the mortality gap in recent years[49,115,116]. Our findings confirm prior reports that antipsychotic medication use is associated with higher CVD risk[13,117,118]. However, due to limitations in the published data, we were unable to explore variations in CVD risk profiles between different antipsychotic medications[13,117-120]. Previous research has suggested that the highest cardio-metabolic risks are associated with clozapine and olanzapine, whilst the lowest risk is with aripiprazole, ziprasidone, lurasidone, amisulpride and high potency typical antipsychotics[13,117-122]. However, in this context it is also important to note that antipsychotic medications can decrease CVD-related mortality, as reported for example in Finnish[79] and Swedish[123] national database studies, that are highly generalizable. These data underscore that symptom control and functional improvement benefit both psychiatric and overall health, as severe psychiatric illness negatively affects lifestyle behaviors, medical care seeking and adherence to medical treatments. Thus, benefits of improved psychiatric status with antipsychotics and other psychotropic agents need to be carefully weighed against their potential for elevated cardiometabolic risk, which differs across available agents[13,117].

Since antipsychotic medication use moderates CVD risk and since antipsychotics are increasingly used as first line treatments for much more prevalent non-psychotic conditions, including bipolar disorder[124] and major depressive disorder with suboptimal response to antidepressant treatment[125], the pool of people at an increased CVD risk is greatly enlarged. Therefore, research on the underlying mechanisms for the increased CVD risk after pharmacotherapy initiation is even more urgently needed to develop more effective and targeted preventive and interventional treatments. Studies should also examine whether different clinical subtypes of depression (i.e., melancholic, psychotic, atypical or undifferentiated) and bipolar disorder (e.g., type 1 or 2, cyclothymic disorder), certain mood states (manic, depressive, mixed or euthymic), or different antipsychotics, antidepressants or mood stabilizers[13] significantly moderate CVD risk.

Furthermore, the pathophysiology underlying the association between SMI and CVD risk is complex and not well understood, clearly requiring further investigation. Emerging evidence suggests that SMI and CVD share pathophysiological features, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, peripheral immune activation, neuro-inflammation, oxidative and nitrosative stress, as well as common genetic links and epigenetic interactions[126]. However, since these different mechanisms probably interact, research that integrates these pathways is urgently needed. Beyond mechanistic evaluations, such studies also need to investigate the general and specific effects of physical health improvements on SMI outcomes.

Future research should also investigate optimal monitoring regimens across stratified patient subgroups as well as the most effective timing and efficacy of primary, secondary and tertiary preventive interventions[120,127]. In this regard, studies should comprehensively assess relevant moderator and mediator variables of CVD risk, including type and duration of specific psychotropic medications use, physical activity (including using passive monitoring via actimetry or mobile phone technology), diet, smoking, body mass index, personal and family history of CVD, in order to identify subgroups of patients who may require different monitoring and or interventions schemes. Long-term follow-up studies are also required to accurately document the emergence of more distal physical and mental health as well as health economic outcomes in relationship to the early identification and management of CVD risk factors and manifest CVD conditions in people with SMI.

Finally, since people with SMI engage in unhealthy lifestyle and often take psychotropic medication for extensive periods, long-term follow-up studies are needed that assess whether current predictor models based on the magnitude of traditional CVD risk factor effects observed in the general population apply or need to be adjusted for the SMI population[93], in whom CVD risk factors also emerge at a far earlier age[117,128].

While this is the most comprehensive meta-analysis of CVD risk in people with SMI conducted to date, we acknowledge several limitations that are largely related to factors in the primary data. First, lifestyle behavior information (e.g., physical activity) was inadequately reported, precluding meta-analytic assessment of these important factors as moderating or mediating variables. People with SMI are less likely than the general population to engage in physical activity and have higher levels of sedentary behaviour[129], smoke more[130], consume diets that are high in saturated fats and refined sugars, while being low in fruit and vegetables[131], all factors relevant for CVD risk. Second, variables such as clinical subtypes of major depressive disorder and bipolar disorder, negative symptom severity in people with schizophrenia, and concomitant or previous use of specific antipsychotics, antidepressants and mood stabilizers were not reported or were insufficiently reported or controlled for in most available studies. Third, as expected when combining observational data[132], many of the results were moderately to highly heterogeneous. However, in accordance with the MOOSE guidelines[133], we conducted meta-regression analyses and were able to explain some of the observed heterogeneity. In addition, all of our results remained robust after adjustment for potential publication bias with the trim and fill analysis.

In conclusion, SMIs pooled together were significantly associated in cross-sectional studies with CVD, coronary heart disease, cerebrovascular disease and CVD-related death. Additionally, in longitudinal studies, each specific diagnostic SMI group was significantly associated with CVD and CVD-related death. Furthermore, schizophrenia was associated with coronary heart disease and cerebrovascular disease, while bipolar disorder was associated with congestive heart failure, and

major depressive disorder was associated with coronary heart disease, cerebrovascular disease, and congestive heart failure.

Importantly, our data confirm that CVDs are associated with an increased risk of mortality in people with SMI, which to a large part explains the shortened life expectancy of people with SMI compared to the general population[2,4,5]. Furthermore, we showed geographical variations in raw CVD prevalence and incidence risk in SMI populations, but no significant regional variance in the difference in CVD risk compared to the region-specific general population. Finally, the fact that antipsychotic use, higher body mass index and baseline CVD significantly increased the risk for CVD morbidity and mortality underscores the urgent need to limit antipsychotic use to those populations truly requiring them, choosing the lowest risk antipsychotic agents first in the treatment algorithm, screening all SMI patients regularly for CVD risk factors and conditions, and addressing any identified abnormalities aggressively.

ACKNOWLEDGEMENTS

B. Stubbs and F. Gaughran receive support from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. F. Gaughran is also funded by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Funding scheme and by the Stanley Medical Research Institute. The views expressed in this publication are those of the authors and not necessarily those of the funding institutions. C.U. Correll, M. Solmi and N. Veronese are joint first authors of the paper.

REFERENCES

1. Chang CK, Hayes RD, Perera G et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PLoS One 2011;6:e19590.
2. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. BMJ 2013;346:f2539.
3. Popovic D, Benabarre A, Crespo JM et al. Risk factors for suicide in schizophrenia: systematic review and clinical recommendations. Acta Psychiatr Scand 2014;130:418-26.
4. Hoang U, Goldacre MJ, Stewart R. Avoidable mortality in people with schizophrenia or bipolar disorder in England. Acta Psychiatr Scand 2013;127:195-201.
5. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72:334-41.
6. Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies. Medicine 2016;95:e2815.
7. Gan Y, Gong Y, Tong X et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. BMC Psychiatry 2014;14:371.
8. Dong JY, Zhang YH, Tong J et al. Depression and risk of stroke: a meta-analysis of prospective studies. Stroke 2012;43:32-7.
9. Van der Kooy K, van Hout H, Marwijk H et al. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry 2007;22:613-26.
10. Prieto ML, Cuellar-Barboza AB, Bobo WV et al. Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis. Acta Psychiatr Scand 2014;130:342-53.
11. Fan Z, Wu Y, Shen J et al. Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. J Psychiatr Res 2013;47:1549-56.
12. Li M, Fan YL, Tang ZY et al. Schizophrenia and risk of stroke: a meta-analysis of cohort studies. Int J Cardiol 2014;173:588-90.
13. Correll CU, Detraux J, De Lepeleire J et al. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14:119-36.
14. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
15. Biostat. Comprehensive Meta-Analysis. https://www.meta-analysis.com.
16. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105-14.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
18. Egger M, Davey Smith G et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
20. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
21. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
22. Beyer J, Kuchibhatla M, Gersing K et al. Medical comorbidity in a bipolar outpatient clinical population. Neuropsychopharmacology 2005;30:401-4.
23. Bresee LC, Majumdar SR, Patten SB et al. Prevalence of cardiovascular risk factors and disease in people with schizophrenia: a population-based study. Schizophr Res 2010;117:75-82.
24. Bresee LC, Majumdar SR, Patten SB et al. Diabetes, cardiovascular disease, and health care use in people with and without schizophrenia. Eur Psychiatry 2011;26:327-32.
25. Chen PH, Gildengers AG, Lee CH et al. High serum sodium level in affective episode associated with coronary heart disease in old adults with bipolar disorder. Int J Psychiatry Med 2015;50:422-33.
26. Curkendall SM, Mo J, Glasser DB et al. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry 2004;65:715-20.
27. Devantier TA, Norgaard BL, Ovrehus KA et al. Coronary plaque volume and composition assessed by computed tomography angiography in patients with late-onset major depression. Psychosomatics 2014;55:243-51.
28. Hagg S, Lindblom Y, Mjorndal T et al. High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. Int Clin Psychopharmacol 2006;21:93-8.

29. Herbst S, Pietrzak RH, Wagner J et al. Lifetime major depression is associated with coronary heart disease in older adults: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med 2007;69:729-34.
30. Huang KL, Su TP, Chen TJ et al. Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. Psychiatry Clin Neurosci 2009;63:401-9.
31. Hyde N, Dodd S, Venugopal K et al. Prevalence of cardiovascular and metabolic events in patients prescribed clozapine: a retrospective observational, clinical cohort study. Curr Drug Saf 2015;10:125-31.
32. Kilbourne AM, Cornelius JR, Han X et al. General-medical conditions in older patients with serious mental illness. Am J Geriatr Psychiatry 2005;13:250-4.
33. Kilbourne AM, Post EP, Bauer MS et al. Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder. J Affect Disord 2007;102:145-51.
34. Lindegard B. Physical illness in severe depressives and psychiatric alcoholics in Gothenburg, Sweden. J Affect Disord 1982;4:383-93.
35. Maina G, D'Ambrosio V, Aguglia A et al. Bipolar disorders and metabolic syndrome: a clinical study in 185 patients. Riv Psichiatr 2010;45:34-40.
36. Morden NE, Lai Z, Goodrich DE et al. Eight-year trends of cardiometabolic morbidity and mortality in patients with schizophrenia. Gen Hosp Psychiatry 2012;34:368-79.
37. Munoli RN, Praharaj SK, Sharma PS. Co-morbidity in bipolar disorder: a retrospective study. Indian J Psychol Med 2014;36:270-5.
38. Nielsen J, Juel J, Alzuhairi KS et al. Unrecognised myocardial infarction in patients with schizophrenia. Acta Neuropsychiatr 2015;27:106-12.
39. Niranjan A, Corujo A, Ziegelstein RC et al. Depression and heart disease in US adults. Gen Hosp Psychiatry 2012;34:254-61.
40. Oreski I, Jakovljevic M, Aukst-Margetic B et al. Comorbidity and multimorbidity in patients with schizophrenia and bipolar disorder: similarities and differencies. Psychiatr Danub 2012;24:80-5.
41. Prieto ML, McElroy SL, Hayes SN et al. Association between history of psychosis and cardiovascular disease in bipolar disorder. Bipolar Disord 2015;17:518-27.
42. Scherrer JF, Xian H, Bucholz KK et al. A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. Psychosom Med 2003;65:548-57.
43. Scott KM, de Jonge P, Alonso J et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. Int J Cardiol 2013;168:5293-9.
44. Shen HN, Lu CL, Yang HH. Increased risks of acute organ dysfunction and mortality in intensive care unit patients with schizophrenia: a nationwide population-based study. Psychosom Med 2011;73:620-6.
45. Smith DJ, Langan J, McLean G et al. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open 2013;3.
46. Smith DJ, Martin D, McLean G et al. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med 2013;11:263.
47. Swain NR, Lim CC, Levinson D et al. Associations between DSM-IV mental disorders and subsequent non-fatal, self-reported stroke. J Psychosom Res 2015;79:130-6.
48. Zilkens RR, Bruce DG, Duke J et al. Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65-84 years): a population based case-control study. Curr Alzheimer Res 2014;11:681-93.
49. Almeida OP, Hankey GJ, Yeap BB et al. Mortality among people with severe mental disorders who reach old age: a longitudinal study of a community-representative sample of 37,892 men. PLoS One 2014;9:e111882.
50. Bremmer MA, Hoogendijk WJ, Deeg DJ et al. Depression in older age is a risk factor for first ischemic cardiac events. Am J Geriatr Psychiatry 2006;14:523-30.
51. Butnoriene J, Bunevicius A, Saudargiene A et al. Metabolic syndrome, major depression, generalized anxiety disorder, and ten-year all-cause and cardiovascular mortality in middle aged and elderly patients. Int J Cardiol 2015;190:360-6.
52. Callaghan RC, Boire MD, Lazo RG et al. Schizophrenia and the incidence of cardiovascular morbidity: a population-based longitudinal study in Ontario, Canada. Schizophr Res 2009;115:325-32.
53. Callaghan RC, Khizar A. The incidence of cardiovascular morbidity among patients with bipolar disorder: a population-based longitudinal study in Ontario, Canada. J Affect Disord 2010;122:118-23.
54. Carney CP, Jones L, Woolson RF. Medical comorbidity in women and men with schizophrenia: a population-based controlled study. J Gen Intern Med 2006;21:1133-7.
55. Chen MH, Li CT, Hsu JW et al. Atopic diseases and subsequent ischemic stroke among patients with schizophrenia: a nationwide longitudinal study. Psychosom Med 2015;77:1031-8.
56. Clouse RE, Lustman PJ, Freedland KE et al. Depression and coronary heart disease in women with diabetes. Psychosom Med 2003;65:376-83.

57. Coryell W, Turvey C, Leon A et al. Persistence of depressive symptoms and cardiovascular death among patients with affective disorder. Psychosom Med 1999;61:755-61.
58. Crump C, Sundquist K, Winkleby MA et al. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 2013;70:931-9.
59. Crump C, Winkleby MA, Sundquist K et al. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013;170:324-33.
60. Davis J, Fujimoto RY, Juarez DT et al. Major depression associated with rates of cardiovascular disease state transitions. Am J Manag Care 2008;14:125-8.
61. Davydow DS, Ribe AR, Pedersen HS et al. Serious mental illness and risk for hospitalizations and rehospitalizations for ambulatory care-sensitive conditions in Denmark: a nationwide population-based cohort study. Med Care 2016;54:90-7.
62. Enger C, Weatherby L, Reynolds RF et al. Serious cardiovascular events and mortality among patients with schizophrenia. J Nerv Ment Dis 2004;192:19-27.
63. Fiedorowicz JG, Solomon DA, Endicott J et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med 2009;71:598-606.
64. Filik R, Sipos A, Kehoe PG et al. The cardiovascular and respiratory health of people with schizophrenia. Acta Psychiatr Scand 2006;113:298-305.
65. Fors BM, Isacson D, Bingefors K et al. Mortality among persons with schizophrenia in Sweden: an epidemiological study. Nord J Psychiatry 2007;61:252-9.
66. Gasse C, Laursen TM, Baune BT. Major depression and first-time hospitalization with ischemic heart disease, cardiac procedures and mortality in the general population: a retrospective Danish population-based cohort study. Eur J Prev Cardiol 2014;21:532-40.
67. Goldstein BI, Schaffer A, Wang S et al. Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. J Clin Psychiatry 2015;76:163-9.
68. Healy D, Le Noury J, Harris M et al. Mortality in schizophrenia and related psychoses: data from two cohorts, 1875-1924 and 1994-2010. BMJ Open 2012;2.
69. Hendrie HC, Tu W, Tabbey R et al. Health outcomes and cost of care among older adults with schizophrenia: a 10-year study using medical records across the continuum of care. Am J Geriatr Psychiatry 2014;22:427-36.
70. Hou PY, Hung GC, Jhong JR et al. Risk factors for sudden cardiac death among patients with schizophrenia. Schizophr Res 2015;168:395-01.
71. Hsieh PH, Hsiao FY, Gau SS et al. Use of antipsychotics and risk of cerebrovascular events in schizophrenic patients: a nested case-control study. J Clin Psychopharmacol 2013;33:299-305.
72. Huang CJ, Hsieh MH, Hou WH et al. Depression, antidepressants, and the risk of coronary heart disease: a population-based cohort study. Int J Cardiol 2013;168:4711-6.
73. Ifteni P, Correll CU, Burtea V et al. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr Res 2014;155:72-6.
74. Jakobsen AH, Foldager L, Parker G et al. Quantifying links between acute myocardial infarction and depression, anxiety and schizophrenia using case register databases. J Affect Disord 2008;109:177-81.
75. Janszky I, Ahnve S, Lundberg I et al. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. J Am Coll Cardiol 2010;56:31-7.
76. Jokinen J, Nordstrom P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. J Affect Disord 2009;116:88-92.
77. Joukamaa M, Heliovaara M, Knekt P et al. Mental disorders and cause-specific mortality. Br J Psychiatry 2001;179:498-502.
78. Kendler KS, Gardner CO, Fiske A et al. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry 2009;66:857-63.
79. Kiviniemi M, Suvisaari J, Koivumaa-Honkanen H et al. Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. Schizophr Res 2013;150:274-80.
80. Lahti M, Tiihonen J, Wildgust H et al. Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. Psychol Med 2012;42:2275-85.
81. Lan CC, Liu CC, Lin CH et al. A reduced risk of stroke with lithium exposure in bipolar disorder: a population-based retrospective cohort study. Bipolar Disord 2015;17:705-14.
82. Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. PLoS One 2011;6:e24597.
83. Laursen TM, Mortensen PB, MacCabe JH et al. Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study. Psychol Med 2014;44:1625-37.
84. Lemogne C, Nabi H, Melchior M et al. Mortality associated with depression as compared with other severe mental disorders: a 20-year follow-up study of the GAZEL cohort. J Psychiatr Res 2013;47:851-7.

85. Li CT, Bai YM, Tu PC et al. Major depressive disorder and stroke risks: a 9-year follow-up population-based, matched cohort study. PLoS One 2012;7:e46818.
86. Lin HC, Chen YH, Lee HC et al. Increased risk of acute myocardial infarction after acute episode of schizophrenia: 6 year follow-up study. Aust N Z J Psychiatry 2010;44:273-9.
87. Lin HC, Tsai SY, Lee HC. Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. J Affect Disord 2007;100:49-54.
88. Lin HC, Hsiao FH, Pfeiffer S et al. An increased risk of stroke among young schizophrenia patients. Schizophr Res 2008;101:234-41.
89. Maina G, Bechon E, Rigardetto S et al. General medical conditions are associated with delay to treatment in patients with bipolar disorder. Psychosomatics 2013;54:437-42.
90. McDermott S, Moran R, Platt T et al. Heart disease, schizophrenia, and affective psychoses: epidemiology of risk in primary care. Community Ment Health J 2005;41:747-55.
91. Murray-Thomas T, Jones ME, Patel D et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. Cardiovasc Psychiatry Neurol 2013;2013:247486.
92. Olfson M, Gerhard T, Huang C et al. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry 2015;72:1172-81.
93. Osborn DP, Hardoon S, Omar RZ et al. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA Psychiatry 2015;72:143-51.
94. Pratt LA, Ford DE, Crum RM et al. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. Circulation 1996;94:3123-9.
95. Prieto ML, Schenck LA, Kruse JL et al. Long-term risk of myocardial infarction and stroke in bipolar I disorder: A population-based Cohort Study. J Affect Disord 2016;194:120-7.
96. Rahman I, Humphreys K, Bennet AM et al. Clinical depression, antidepressant use and risk of future cardiovascular disease. Eur J Epidemiol 2013;28:589-95.
97. Ramsey CM, Leoutsakos JM, Mayer LS et al. History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 year follow-up from the Baltimore Epidemiologic Catchment Area Study. J Affect Disord 2010;125:35-41.
98. Saint Onge JM, Krueger PM, Rogers RG. The relationship between major depression and nonsuicide mortality for U.S. adults: the importance of health behaviors. J Gerontol B Psychol Sci Soc Sci 2014;69:622-32.
99. Scherrer JF, Garfield LD, Chrusciel T et al. Increased risk of myocardial infarction in depressed patients with type 2 diabetes. Diabetes Care 2011;34:1729-34.
100. Schoepf D, Heun R. Bipolar disorder and comorbidity: increased prevalence and increased relevance of comorbidity for hospital-based mortality during a 12.5-year observation period in general hospital admissions. J Affect Disord 2014;169:170-8.
101. Schoepf D, Uppal H, Potluri R et al. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. Eur Arch Psychiatry Clin Neurosci 2014;264:3-28.
102. Shah AJ, Veledar E, Hong Y et al. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. Arch Gen Psychiatry 2011;68:1135-42.
103. Stewart JC, Perkins AJ, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: data from the IMPACT randomized controlled trial. Psychosom Med 2014;76:29-37.
104. Surtees PG, Wainwright NW, Luben RN et al. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. Am J Psychiatry 2008;165:515-23.
105. Ting RZ, Lau ES, Ozaki R et al. High risk for cardiovascular disease in Chinese type 2 diabetic patients with major depression--a 7-year prospective analysis of the Hong Kong Diabetes Registry. J Affect Disord 2013;149:129-35.
106. Torniainen M, Mittendorfer-Rutz E, Tanskanen A et al. Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull 2015;41:656-63.
107. Tsai KY, Lee CC, Chou YM et al. The incidence and relative risk of stroke in patients with schizophrenia: a five-year follow-up study. Schizophr Res 2012;138:41-7.
108. Tsan JY, Stock EM, Gonzalez JM et al. Mortality and guideline-concordant care for older patients with schizophrenia: a retrospective longitudinal study. BMC Med 2012;10:147.
109. van Marwijk HW, van der Kooy KG, Stehouwer CD et al. Depression increases the onset of cardiovascular disease over and above other determinants in older primary care patients, a cohort study. BMC Cardiovasc Disord 2015;15:40.
110. Weeke A, Juel K, Vaeth M. Cardiovascular death and manic-depressive psychosis. J Affect Disord 1987;13:287-92.

111. Westman J, Hallgren J, Wahlbeck K et al. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. BMJ Open 2013;3.
112. Wu HC, Chou FH, Tsai KY et al. The incidence and relative risk of stroke among patients with bipolar disorder: a seven-year follow-up study. PLoS One 2013;8:e73037.
113. Wu SI, Chen SC, Liu SI et al. Relative risk of acute myocardial infarction in people with schizophrenia and bipolar disorder: a population-based cohort study. PLoS One 2015;10:e0134763.
114. Vancampfort D, Stubbs B, Mitchell AJ et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 2015;14:339-47.
115. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol 2014;10:425-48.
116. Nielsen RE, Uggerby AS, Jensen SO et al. Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades – a Danish nationwide study from 1980 to 2010. Schizophr Res 2013;146:22-27.
117. De Hert M, Detraux J, van Winkel R et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011;8:114-26.
118. Correll CU, Joffe BI, Rosen LM et al. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. World Psychiatry 2015;14:56-63.
119. Vancampfort D, Correll CU, Wampers M et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychol Med 2014;44:2017-28.
120. De Hert M, Correll CU, Bobes J et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011;10:52-77.
121. Correll CU, Robinson DG, Schooler NR et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatry 2014;71:1350-63.
122. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. Neuropsychopharmacology 2010;35:1997-2004.
123. Tiihonen J, Mittendorfer-Rutz E, Torniainen M et al. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. Am J Psychiatry 2016;173:600-6.
124. Pillarella J, Higashi A, Alexander GC et al. Trends in use of second-generation antipsychotics for treatment of bipolar disorder in the United States, 1998-2009. Psychiatr Serv 2012;63:83-6.
125. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry 2010;71 Suppl E1:e04.
126. Manu P, Correll CU, Wampers M et al. Markers of inflammation in schizophrenia: association vs. causation. World Psychiatry 2014;13:189-92.
127. De Hert M, Cohen D, Bobes J et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 2011;10:138-51.
128. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends Mol Med 2011;17:97-107.
129. Stubbs B, Firth J, Berry A et al. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. Schizophr Res 2016;176:431-40.
130. Dickerson F, Stallings CR, Origoni AE et al. Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. Psychiatr Serv 2013;64:44-50.
131. Bly MJ, Taylor SF, Dalack G et al. Metabolic syndrome in bipolar disorder and schizophrenia: dietary and lifestyle factors compared to the general population. Bipolar Disord 2014;16:277-88.
132. Speyer H, Norgaard HCB, Birk M et al. The CHANGE trial: no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity. World Psychiatry 2016;15:155-65.
133. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

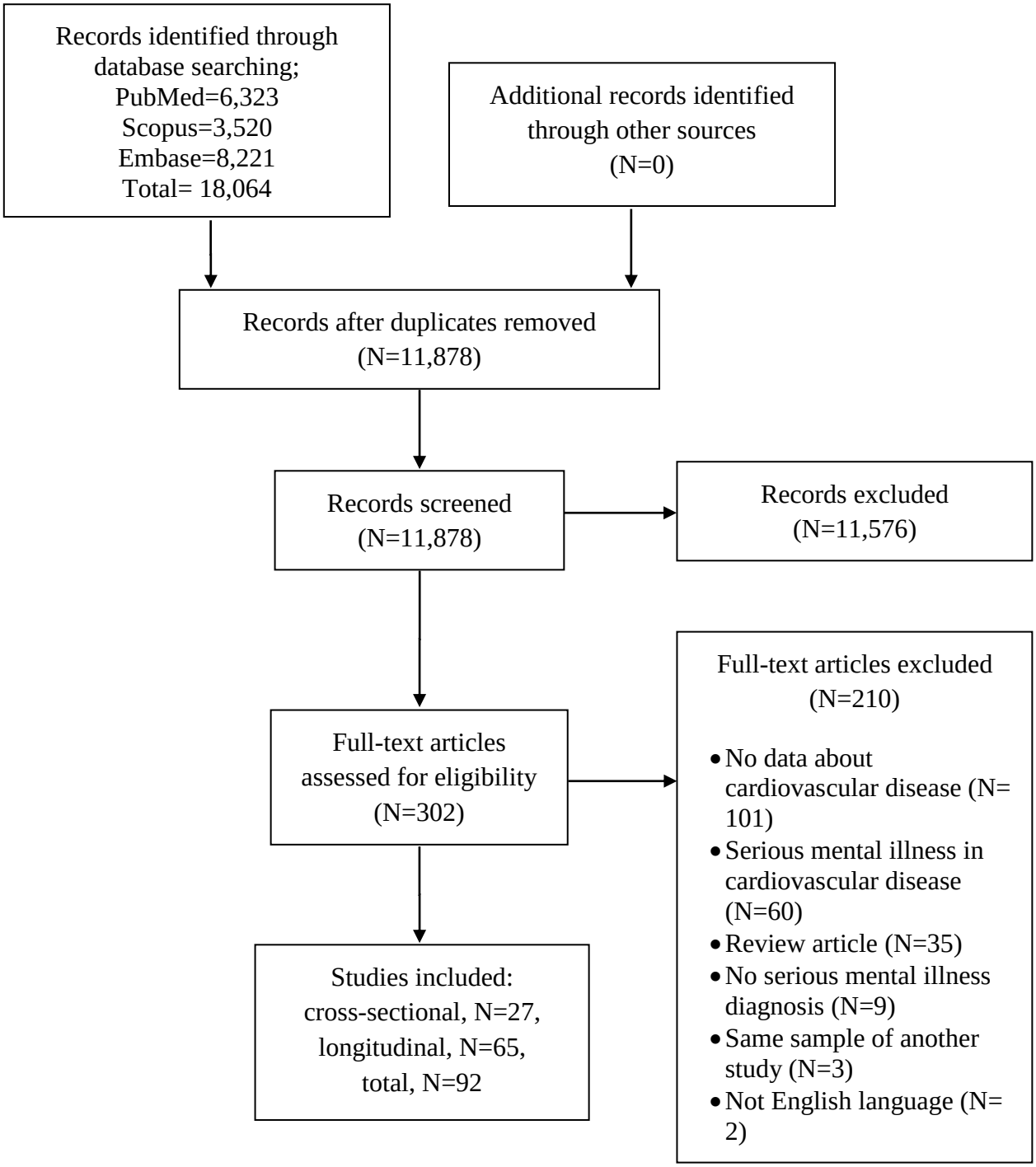

Figure 1 PRISMA flow chart

Table 1 Cross-sectional studies: characteristics of included studies and samples

Study	Country	N cases	N controls	Period of data collection	SMI definition	Inclusion criteria for cases	Number of covariates
Beyer et al[22]	USA	1,379	-	2001-2002	Medical records	Bipolar disorder	-
Breese et al[23]	Canada	28,775	2,281,636	1995-2006	ICD-9, 10	Schizophrenia	4
Bresee et al[24]	Canada	399	120,044	2005	Medical records	Schizophrenia	11
Chen et al[25]	Taiwan	80	-	2015	DSM-IV	Bipolar disorder, >60 years	-
Curkendall et al[26]	Canada	3,022	12,088	1994-1999	ICD-9	Schizophrenia	7
Devantier et al[27]	Denmark	28	27	2009-2011	ICD-10	Major depressive disorder, late onset	-
Hagg et al[28]	Sweden	269	-	2000-2003	DSM-IV	Schizophrenia, 20-69 years	-
Herbst et al[29]	USA	10,573 total population		2001-2002	DSM-IV	Major depressive disorder, >60 years	11
Huang et al[30]	Taiwan	117,987	21,356,304	2000-2003	ICD-9	Bipolar disorder or major depressive disorder	1
Hyde et al[31]	Australia	355	-	2008-2012	Medical records	Severe mental illness, prescribed clozapine	-
Kilbourne et al[32]	USA	8,083	-	2001	ICD-9	Severe mental illness, >60 years	-
Kilbourne et al[33]	USA	9,705	5,353	2000-2001	ICD-9	Bipolar disorder or severe mental illness, male	3
Lindergard[34]	Sweden	368	87,176	1966-1979	ICD-9, DSM-III	Major depressive disorder or bipolar disorder	-
Maina et al[35]	Italy	185	-	2006-2008	DSM-IV	Severe mental illness	-

Study	Country	N cases	N controls	Period of data collection	SMI definition	Inclusion criteria for cases	Number of covariates
Morden et al[36]	Canada	65,362	65,362	2000-2007	ICD-9	Schizophrenia	4
Munoli et al[37]	India	120	-	2011	ICD-10	Bipolar disorder	-
Nielsen et al[38]	Denmark	937	-	1969-2014	ICD-10	Schizophrenia	-
Niranjan et al[39]	USA	5,695	34,979	2007	DSM-IV	Major depressive disorder	6
Oreski et al[40]	Croatia	289	192	2011	ICD-10	Bipolar disorder or schizophrenia	-
Prieto et al[41]	USA	988	-	2009-2013	DSM-IV	Severe mental illness	-
Scherrer et al[42]	USA	628	6,903	1990-1992	DSM-III	Major depressive disorder, male twins	-
Scott et al[43]	Multicenter	52,095 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	6
Shen et al[44]	Taiwan	203	2,036	2005-2007	ICD-9	Schizophrenia, in intensive care unit	6
Smith et al[45]	UK	9,677	1,414,701	2007	Medical records	Schizophrenia	3
Smith et al[46]	UK	2,582	1,421,796	2007	Medical records	Bipolar disorder	2
Swain et al[47]	Multicenter	45,288 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	7
Zilkens et al[48]	Australia	656	349	2000-2009	ICD-8,9,10	Major depressive disorder, 65-84 years, developing dementia	-

SMI – severe mental illness

Table 2 Longitudinal studies: characteristics of included studies and samples

Study	Country	N cases	N controls	Period of data collection	SMI Definition	Inclusion criteria for cases	Number of covariates
Almeida et al[49]	Australia	1,503	35,691	1996-2010	ICD-9	Schizophrenia, bipolar disorder or major depressive disorder, 65-85 years, male	8
Bremmer et al[50]	The Netherlands	41	2,080	1992-2000	DSM-III	Major depressive disorder, >55 years	13
Butnoriene et al[51]	Lithuania	184	369	2003-2004	DSM-IV	Major depressive disorder, >45 years	4
Callaghan et al[52]	Canada	5,999	5,999	2002-2006	Medical records	Bipolar disorder	6
Callaghan et al[53]	Canada	9,815	9,815	2002-2006	ICD-10	Bipolar disorder	8
Carney et al[54]	USA	1,074	726,262	1996-2001	ICD-9	Schizophrenia or schizoaffective disorder	4
Chen et al[55]	Taiwan	63,913	63,913	2002-2008	ICD-9	Schizophrenia	8
Clouse et al[56]	USA	16	60	1982-1992	DSM-III	Major depressive disorder with diabetes	7
Coryell et al[57]	USA	903	-	1998-1999	RDC	Severe mental illness	-
Crump et al[58]	Sweden	6,618	6,580,418	2003-2009	ICD-10	Bipolar disorder	6
Crump et al[59]	Sweden	8,277	6,097,834	2003-2009	ICD-10	Schizophrenia, >25 years	6
Davis et al[60]	Hawaii	280	39,000	1999-2005	Medical records	Major depressive disorder	5
Davydow et al[61]	Denmark	681,37	5,912,158	1999-2013	ICD-9	Schizophrenia, schizoaffective disorder or bipolar disorder	5
Enger et al[62]	USA	1,920	9,600	1995-1999	ICD-9	Schizophrenia, on antipsychotic treatment, 15-64 years	-
Fiedorowicz et al[63]	USA	288	147	1978-1981	RDC	Bipolar disorder	8
Filik et al[64]	UK	482	1,998	1999-2002	DSM-IV	Schizophrenia, schizophreniform or schizoaffective disorder	6
Fors et al[65]	Sweden	255	1,275	1981-1991	DSM-II	Schizophrenia	3
Gasse et al[66]	Denmark	873,898	52,693,301	1995-2009	ICD-8,10	Severe mental illness (affective psychoses)	22
Goldstein et al[67]	USA	5,835	26,266	2001-2005	DSM-IV	Bipolar disorder or major depressive disorder	8

Healy et al[68]	UK	1,429	-	1875-1924; 1994-2010	Medical records	Schizophrenia	-
Hendrie et al[69]	USA	757	30,831	1999-2008	ICD-9	Schizophrenia, >65 years	-
Hou et al[70]	Taiwan	8,264	-	1985-2008	DSM-III or IV, ICD-9	Schizophrenia	-
Hsieh et al[71]	Taiwan	9,715	-	2001-2009	ICD-9	Schizophrenia	10
Huang et al[72]	Taiwan	7,937	31,748	1996-2006	ICD9	Major depressive disorder	9
Ifteni et al[73]	Romania	7,189	-	1989-2011	DSM-IV	Schizophrenia, inpatients	-
Jakobsen et al[74]	Denmark	74,759	338,747	1977-2000	ICD-8,10	Schizophrenia or major depressive disorder	2
Janszky et al[75]	Sweden	646	48,675	1969-2007	ICD-8	Major depressive disorder, 18-20 years	7
Jokinen et al[76]	Sweden	346	-	1980-2005	DSM-IV	Major depressive disorder or bipolar disorder	-
Joukamaa et al[77]	Finland	606	8,000	1977-1994	Medical records	Schizophrenia, mood disorder or severe mental illness	1
Kendler et al[78]	Sweden	5,647	24,727	1998-2003	ICD-10	Major depressive disorder, twins	-
Kiviniemi et al[79]	Finland	6,987	-	1998-2003	ICD-9	Schizophrenia, first onset	-
Lahti et al[80]	Finland	204	11,880	1969-2004	ICD-8,9,10	Schizophrenia	5
Lan et al[81]	Taiwan	3,681	-	2001-2006	ICD-9	Bipolar disorder	-
Laursen et al[82]	Denmark	22,294	2,411,852	1995-2007	ICD-8,10	Schizophrenia or bipolar disorder, 15-52 years	3
Laursen et al[83]	Denmark	1,454	59,256	1995-2006	ICD-8,10	Schizophrenia or bipolar disorder	4
Lemogne et al[84]	France	4,336	16,621	1990-2010	ICD-9,10	Depression or severe mental illness (bipolar disorder, psychosis)	6
Li et al[85]	Taiwan	1,003	4,012	1996-2009	ICD-9	Major depressive disorder	6
Lin et al[86]	Taiwan	7,353	22,059	2000-2006	ICD-9	Schizophrenia	8
Lin et al[87]	Taiwan	2,289	16,413	1998-2003	ICD-9	Bipolar disorder	10
Lin et al[88]	Taiwan	5,001	10,002	1998-2003	ICD-9	Schizophrenia, <45 years	9
Maina et al[89]	Italy	309	-	2003-2011	DSM-IV	Bipolar disorder	-
McDermott et	USA	503	2,083	1990-2003	ICD-9	Schizophrenia or severe mental illness	9

al[90]							
Murray-Thomas et al[91]	UK	232,132	193,920	1997-2001	ICD-10	Schizophrenia, bipolar disorder or major depressive disorder	2
Olfson et al[92]	USA	1,138,853	-	2001-2007	ICD-10	Schizophrenia, 20-64 years	4
Osborn et al[93]	UK	38,824	-	1995-2010	Medical records	Bipolar disorder or severe mental illness, 30-90 years	-
Pratt et al[94]	USA	73	1107	1981-1994	DSM-III	Major depressive disorder	11
Prieto et al[95]	USA	334	334	1966-1996	DSM-IV	Bipolar disorder	4
Rahman et al[96]	Sweden	6,822	29,832	1998-2002	ICD-7,8,9,10	Major depressive disorder, twin population study	7
Ramsey et al[97]	USA	129	1,339	1981-1982	DSM-III	Bipolar disorder or major depressive disorder	6
Saint Onge et al[98]	USA	548	10,821	1999-2006	ICD	Major depressive disorder	11
Scherrer et al[99]	USA	77,568	214,749	1999-2007	ICD-9	Major depressive disorder, 25-80 years	4
Schoepf et al[100]	UK	1,418	14,180	2000-2012	ICD-10	Schizophrenia, inpatients	-
Schoepf et al[101]	UK	621	6,210	2000-2012	ICD-10	Bipolar disorder	-
Shah et al[102]	USA	538	7,103	1988-2006	DSM-III	Major depressive disorder or bipolar disorder, 17-39 years	14
Stewart et al[103]	USA	235	-	NA	ICD-9	Major depressive disorder	-
Surtees et al[104]	UK	3,057	16,592	1996-2008	DSM-IV	Major depressive disorder, 45-80 years	11
Ting et al[105]	China	153	7,682	1996-2008	DSM-IV	Major depressive disorder with diabetes	18
Torniainen et al[106]	Sweden	21,492	214,920	2006-2015	ICD-10	Schizophrenia, 17-65 years	2
Tsai et al[107]	Taiwan	80,569	241,707	1999-2003	ICD-9	Schizophrenia	8
Tsan et al[108]	USA	49,173	-	2002-2009	ICD-9	Schizophrenia	-
van Marwijk et al[109]	The Netherlands	143	139	2002-2003	DSM-IV	Major depressive disorder, >55 years	-
Weeke et al[110]	Denmark	3,795	-	1950-1957; 1969-1977	ICD-8	Bipolar disorder	-
Westman et al[111]	Sweden	17,101	10,631,208	1987-2006	ICD-10	Bipolar disorder	3
Wu et al[112]	Taiwan	16,821	67,284	1999-2010	ICD-9	Bipolar disorder	9

Wu et al[113]	Taiwan	70,225	207,592	1996-2007	ICD-9	Schizophrenia or bipolar disorder	8

SMI – severe mental illness, RDC – Research Diagnostic Criteria

Table 3 Meta-analysis of cross-sectional studies: unadjusted and adjusted odds ratios

	Meta-analysis of unadjusted odds ratios								Meta-analysis of covariate adjusted odds ratios							
	N studies	N participants		Unadjusted odds ratios				Hetero-geneity	N studies	N participants		Adjusted odds ratios				Hetero-geneity
Disorder		**Patients**	**Controls**	**OR**	**95% CI**		**p**	**I^2**		**Patients**	**Controls**	**OR**	**95% CI**		**p**	**I^2**
Cardiovascular disease																
Bipolar disorder	4	19,562	1,526,110	**1.73**	**1.11**	**2.71**	**0.02**	91	4	2,640	1,423,135	1.28	0.90	1.80	0.17	52
Major depressive disorder	3	1,577	47,851	**2.08**	**1.51**	**2.88**	**<0.001**	58	7	7,050	43,570	**1.75**	**1.36**	**2.26**	**<0.001**	69
Schizophrenia	10	190,584	4,100,315	1.23	0.92	1.65	0.16	99	5	42,076	3,860,505	1.38	0.93	2.05	0.11	96
Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	14	211,869	7,808,603	**1.59[a]**	**1.32**	**1.91**	**<0.001**	99	11	51,766	5,325,871	**1.53[e]**	**1.27**	**1.83**	**<0.001**	94
Coronary heart disease																
Bipolar disorder	3	19,504	1,524,771	**1.75**	**1.11**	**2.77**	**0.02**	94	1	2,582	1,421,796	0.94	0.79	1.11	0.49	-
Major depressive disorder	1	958	35,691	**2.44**	**2.13**	**2.79**	**<0.0001**	-	3	6,323	41,882	**2.52**	**1.81**	**3.52**	**<0.001**	93
Schizophrenia	8	187,359	4,086,191	1.03	0.85	1.25	0.76	98	1	399	120,044	**1.52**	**1.48**	**1.56**	**<0.001**	-
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-		-	-	-	-	-	-
Pooled	8	207,967	4,160,030	**1.80[b]**	**1.62**	**2.00**	**<0.001**	98	5	9,304	1,583,722	**1.51[f]**	**1.47**	**1.55**	**<0.001**	90
Cerebrovascular disease																
Bipolar disorder	3	2,741	1,458,826	**1.68**	**1.07**	**2.63**	**0.03**	47	2	2,582	1,421,796	1.06	0.85	1.31	0.62	0
Major depressive disorder	3	1,577	47,851	**2.24**	**1.33**	**3.79**	**0.003**	81	2	656	349	1.64	0.96	2.78	0.07	72
Schizophrenia	5	41,071	37,77,039	**1.63**	**1.19**	**2.24**	**0.003**	96	3	32,196	2,413,768	**2.05**	**1.59**	**2.64**	**<0.001**	61
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-	-	-	-	--	-	-	-
Pooled	10	45,535	5,454,785	**1.63[c]**	**1.31**	**2.02**	**<0.0001**	93	6	35,434	3,835,913	**1.42[g]**	**1.21**	**1.66**	**<0.001**	90
Congestive heart failure																
Bipolar disorder	1	2,582	1,421,796	**1.38**	**1.03**	**1.84**	**0.03**	-	1	2,582	1,421,796	1.11	0.80	1.54	0.53	0
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	5	40,984	3,743,431	**1.71**	**1.36**	**2.15**	**<0.001**	92	3	41,474	5,708,425	**1.60**	**1.06**	**2.40**	**0.02**	97

Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	6	43,712	5,167,189	**1.57[d]**	**1.32**	**1.87**	**<0.001**	88	4	44,056	7,130,221	1.28[h]	0.99	1.65	0.06	96

Bold values represent significant results

Egger test for bias: [a]2.24, p=0.53; [b]6.41, p=0.03 (Duval & Tweedie trim-and-fill procedure adjusted OR: 1.35, 95% CI: 0.98-1.83); [c]–1.69, p=0.24; [d]–2.39, p=0.15; [e]–1.73, p=0.18; [f]0.17, p=0.93; [g]–2.59, p=0.07; [h]–5.26, p=0.20

Table 4 Meta-analysis of longitudinal studies with publication bias assessment

	Meta-analysis of unadjusted relative risk								Meta-analysis of covariate adjusted hazard ratio							
	N studies	N participants		Unadjusted relative risk				Hetero-geneity	N studies	N participants		Adjusted hazard ratio				Hetero-geneity
Disorder		**Patients**	**Controls**	**RR**	**95% CI**		**p**	**I^2**		**Patients**	**Controls**	**HR**	**95% CI**		**p**	**I^2**
Cardiovascular disease																
Bipolar disorder	12	66,549	9,606,575	**1.50**	**1.28**	**1.75**	**<0.0001**	76	10	91,187	6,967,728	**1.57**	**1.28**	**1.93**	**<0.0001**	91
Major depressive disorder	13	328,,431	800,718	1.29	0.92	1.81	0.14	99	18	282,621	682,045	**1.72**	**1.48**	**2.00**	**<0.0001**	67
Schizophrenia	16	361294	16,096,125	**1.21**	**1.006**	**1.45**	**0.04**	98	14	296,778	7,176,374	**1.95**	**1.41**	**2.70**	**<0.0001**	99
Severe mental illnesses	2	874022	52,709,922	**2.44**	**1.13**	**5.25**	**0.02**	74	3	798	31,724	**3.24**	**2.15**	**4.88**	**<0.0001**	0
Pooled	33	1,630,296	76,031,192	**1.38**[a]	**1.23**	**1.54**	**<0.0001**	98	31	671,384	14,335,203	**1.78**[g]	**1.60**	**1.98**	**<0.0001**	95
Coronary heart disease																
Bipolar disorder	4	25,286	9,200,196	**1.95**	**1.20**	**3.17**	**0.007**	96	4	19,129	6,789,683	1.16	0.76	1.78	0.49	87
Major depressive disorder	6	14,3671	515,187	1.15	0.71	1.85	0.57	98	9	99,028	392,210	**1.63**	**1.33**	**2.00**	**<0.0001**	80
Schizophrenia	8	169,507	15,446,625	0.93	0.81	1.08	0.33	87	5	75,860	6,348,965	**1.59**	**1.08**	**2.35**	**0.02**	95
Severe mental illnesses	1	873,898	52,693,301	**1.80**	**1.74**	**1.86**	**<0.0001**	-	-	-	-	-	-	-	-	-
Pooled	17	1,212,362	75,235,865	**1.75**[b]	**1.69**	**1.80**	**<0.0001**	99	18	194,017	13,530,858	**1.54**[h]	**1.30**	**1.82**	**<0.0001**	92
Cerebrovascular disease																
Bipolar disorder	6	32,898	9,082,511	**1.92**	**1.13**	**3.26**	**0.02**	97	4	23,831	6,649,375	1.60	0.99	2.57	0.05	85
Major depressive disorder	4	8,121	41,665	**1.55**	**1.02**	**2.35**	**0.04**	77	3	7,046	38,853	**2.04**	**1.05**	**3.96**	**0.04**	74
Schizophrenia	8	243,254	15,475,608	**1.48**	**1.21**	**1.81**	**<0.0001**	96	5	157,964	6,425,336	**1.57**	**1.09**	**2.25**	**0.02**	95
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Pooled	17	284,273	22,187,932	**1.53[c]**	**1.29**	**1.82**	**<0.0001**	96	11	188,841	13,113,564	**1.64[i]**	**1.26**	**2.14**	**<0.0001**	90
Congestive heart failure																
Bipolar disorder	1	6,215	2,411,852	**11.52**	**9.37**	**23.14**	**<0.0001**	-	1	58	1,339	**2.27**	**1.49**	**3.45**	**<0.0001**	0
Major depressive disorder	-	-	-	-	-	-	-	-	2	351	40,339	**2.02**	**1.48**	**2.75**	**<0.0001**	0
Schizophrenia	3	85,290	9,050,272	**1.80**	**1.15**	**2.79**	**0.009**	84	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	4	91,505	11,459,059	**8.24[d]**	**6.84**	**9.94**	**<0.0001**	99	2	409	41,678	**2.10**	**1.64**	**2.70**	**<0.0001**	0
Peripheral vascular disease																
Bipolar disorder	1	6,215	2,411,852	**3.44**	**2.70**	**4.38**	**<0.0001**	-	-	-	-	-	-	-	-	-
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	3	85,290	9,050,272	0.96	0.43	2.17	0.92	93	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	3	91,505	11,402,868	**3.11[e]**	**2.46**	**3.91**	**<0.0001**	98	-	-	-	-	-	-	-	-
Death due to cardiovascular disease																
Bipolar disorder	5	37,144	356,298	1.31	0.94	1.83	0.11	75	3	17,420	162,231	**1.65**	**1.10**	**2.47**	**0.02**	88
Major depressive disorder	5	18,112	283,746	1.30	0.59	2.86	0.51	99	7	183,297	282,014	**1.63**	**1.25**	**2.13**	**<0.0001**	81
Schizophrenia	9	53,779	7,179,454	1.26	0.84	1.90	0.27	96	9	152,690	6,872,808	**2.45**	**1.64**	**3.65**	**<0.0001**	96
Severe mental illnesses	3	874,146	52,714,134	**2.99**	**2.84**	**3.13**	**<0.0001**	0	3	798	31,724	**2.75**	**1.32**	**5.73**	**0.007**	75
Pooled	18	1,151,181	60,287,400	**2.89[f]**	**2.75**	**3.03**	**<0.0001**	99	16	353,407	7,317,053	**1.85[l]**	**1.53**	**2.24**	**<0.0001**	95

Egger test for bias: [a]–0.44, p=0.80; [b]–1.24, p=0.71; [c]0.03, p=0.96; [d]8.07, p=0.37; [e]3.08, p=0.60; [f]–3.66, p=0.20; [g]1.16, p=0.31; [h]–0.13, p=0.92; [i]2.57, p=0.07; [l]–1.19, p=0.43

Table 5 Quality assessment of included studies

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Cross-sectional studies						
Curkendall et al[26]	Y	Y	Y	Y	Y	N
Hagg et al[28]	Y	N	N	N	Y	N
Breese et al[23]	Y	Y	N	Y	Y	N
Devantier et al[27]	Y	Y	Y	N	Y	N
Lindergard[34]	Y	Y	N	N	N	N
Niranjan et al[39]	Y	Y	N	Y	Y	N
Scherrer et al[42]	Y	Y	N	N	N	N
Herbst et al[29]	Y	Y	N	Y	N	N
Huang et al[30]	Y	Y	N	Y	Y	N
Swain et al[47]	Y	Y	N	Y	N	N
Scott et al[43]	Y	Y	N	Y	N	N
Prieto et al[41]	Y	N	N	N	Y	N
Munoli et al[37]	Y	N	N	N	Y	N
Smith et al[45]	Y	Y	N	Y	Y	N
Maina et al[35]	Y	N	N	N	Y	N
Beyer et al[22]	Y	N	N	N	Y	N
Oreski et al[40]	Y	Y	N	N	Y	N
Nielsen et al[38]	Y	N	N	N	Y	N
Zilkens et al[48]	Y	Y	Y	N	N	N
Smith et al[46]	Y	Y	N	Y	Y	N
Kilbourne et al[32]	Y	N	N	N	Y	N
Hyde et al[31]	Y	N	N	N	Y	N
Bresee et al[24]	Y	Y	N	Y	Y	N
Morden et al[36]	Y	Y	Y	Y	Y	N
Kilbourne et al[33]	Y	Y	N	Y	Y	N
Chen et al[25]	Y	N	N	N	Y	N
Shen et al[44]	Y	Y	Y	Y	Y	N
Longitudinal studies						
Enger et al[62]	Y	Y	Y	Y	Y	N
Filik et al[64]	Y	Y	Y	N	Y	N
Fors et al[65]	Y	Y	Y	Y	N	Y
Callaghan et al[52]	Y	Y	Y	Y	Y	N
Lin et al[86]	Y	Y	Y	Y	Y	Y
Lahti et al[80]	Y	Y	Y	N	Y	Y
Joukamaa et al[77]	Y	Y	Y	N	N	Y
Lemogne et al[84]	Y	Y	Y	N	Y	Y
Ting et al[105]	Y	Y	Y	N	Y	Y
Saint Onge et al[98]	Y	Y	Y	N	Y	Y
Stewart et al[103]	Y	Y	N	N	N	Y
Coryell et al[57]	Y	Y	N	N	N	Y

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Clouse et al[56]	Y	Y	Y	N	Y	Y
Li et al[85]	Y	Y	Y	Y	Y	Y
Gasse et al[66]	Y	Y	Y	N	N	Y
Butnoriene et al[51]	Y	Y	Y	N	N	Y
Bremmer et al[50]	Y	Y	Y	N	Y	Y
Jakobsen et al[74]	Y	Y	Y	Y	N	Y
Davis et al[60]	Y	Y	Y	N	Y	N
Jokinen et al[76]	Y	Y	N	N	N	Y
Kendler et al[78]	Y	Y	Y	N	N	Y
Shah et al[102]	Y	Y	Y	N	Y	Y
Surtees et al[104]	Y	Y	Y	N	N	Y
van Marwijk et al[109]	Y	Y	Y	Y	Y	N
Scherrer et al[99]	Y	Y	Y	N	Y	Y
Wu et al[113]	Y	Y	Y	N	Y	Y
Goldstein et al[67]	Y	Y	Y	N	Y	N
Schoepf et al[100]	Y	Y	Y	Y	N	Y
Almeida et al[49]	Y	Y	Y	N	Y	Y
Laursen et al[83]	Y	Y	Y	N	N	Y
Murray-Thomas et al[91]	Y	Y	Y	N	N	N
Crump et al[58]	Y	Y	Y	N	N	Y
Westman et al[111]	Y	Y	Y	N	N	Y
Maina et al[89]	Y	Y	N	N	N	Y
Weeke et al[110]	Y	Y	N	N	N	N
Fiedorowicz et al[63]	Y	Y	Y	N	Y	Y
Callaghan et al[53]	Y	Y	Y	Y	Y	N
Osborn et al[93]	Y	Y	Y	N	Y	Y
Chen et al[55]	Y	Y	Y	Y	Y	Y
Hou et al[70]	Y	Y	N	N	N	Y
Ifteni et al[73]	Y	Y	N	N	N	Y
Schoepf et al[101]	Y	Y	Y	Y	Y	Y
Hendrie et al[69]	Y	Y	Y	N	Y	Y
Kiviniemi et al[79]	Y	Y	N	N	N	Y
Crump et al[59]	Y	Y	Y	N	Y	Y
Wu et al[112]	Y	Y	Y	Y	Y	Y
Torniainen et al[106]	Y	Y	Y	Y	N	Y
Hsieh et al[71]	Y	Y	N	N	N	N
Tsan et al[108]	Y	Y	N	N	Y	Y
Healy et al[68]	Y	Y	N	N	N	Y
Prieto et al[95]	Y	Y	Y	Y	Y	Y
Davydow et al[61]	Y	Y	Y	N	N	Y
Lan et al[81]	Y	Y	N	N	Y	Y
Olfson et al[92]	Y	Y	N	N	N	Y
Tsai et al[107]	Y	Y	Y	Y	Y	Y

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Ramsey et al[97]	Y	Y	Y	N	Y	Y
Rahman et al[96]	Y	Y	Y	Y	Y	N
Pratt et al[94]	Y	Y	Y	N	Y	Y
McDermott et al[90]	Y	Y	Y	N	N	Y
Lin et al[88]	Y	Y	Y	Y	Y	Y
Lin et al[87]	Y	Y	Y	Y	Y	Y
Laursen et al[82]	Y	Y	Y	N	N	Y
Janszky et al[75]	Y	Y	Y	N	Y	Y
Huang et al[72]	Y	Y	Y	Y	Y	Y
Carney et al[54]	Y	Y	Y	N	Y	N

N – no, Y – yes

Table 6 Prevalence and incidence of cardiovascular disease (CVD) in severe mental illness stratified by region

Regional strata	Analysis details	Prevalence of CVD	Incidence of CVD	Risk ratios for incident CVD	Adjusted hazard ratios for incident CVD
Asia	Pooled estimate, % (95% CI)	5.4 (4.3-6.7)	2.6 (1.9-3.6)	1.63 (1.31-2.04)	1.75 (1.38-2.22)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	98 (<0.0001)	100 (<0.0001)	99 (<0.0001)	96 (<0.0001)
	N comparisons	8	12	9	10
Europe	Pooled estimate, % (95% CI)	9.7 (6.5-14.2)	3.4 (2.2-5.3)	1.17 (0.96-1.42)	1.88 (1.44-2.46)
	p value	<0.0001	<0.0001	0.11	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	96 (<0.0001)
	N comparisons	9	35	20	22
North America	Pooled estimate, % (95% CI)	14.6 (12.0-17.7)	4.6 (3.4-6.2)	1.39 (0.91-2.12)	1.88 (1.62-2.19)
	p value	<0.0001	<0.0001	0.13	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	62 (0.003)
	N comparisons	17	15	11	11
Oceania	Pooled estimate, % (95% CI)	20.6 (10.9-35.4)	26.3 (24.1-28.6)	1.52 (1.40-1.66)	1.58 (1.41-1.78)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	0 (0.72)	0 (0.84)
	N comparisons	4	3	3	3
	p (difference between regions)	<0.0001	<0.0001	0.08	0.29